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SYSTEMATIC REVIEW

Factors Contributing to Chronic Ankle Instability: A Systematic Review and Meta-Analysis of Systematic Reviews

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Abstract
Background Many factors are thought to contribute to chronic ankle instability (CAI). Multiple systematic reviews have synthesised the available evidence to identify the primary contributing factors. However, readers are now faced with several systematic reviews that present conflicting findings.
Objective The aim of this systematic review and meta-analysis was to establish the statistical significance and effect size of primary factors contributing to CAI and to identify likely reasons for inconsistencies in the literature.
Methods Relevant health databases were searched: CINAHL, MEDLINE, PubMed, Scopus and SPORTDiscus. Systematic reviews were included if they answered a focused research question, clearly defined the search strategy criteria and study selection/inclusion and completed a comprehensive search of the literature. Included reviews needed to be published in a peer-reviewed journal and needed to review observational studies of factors and/or characteristics of persons with CAI, with or without meta-analysis. There was no language restriction. Studies using a non-systematic review methodology (e.g. primary studies and narrative reviews) were excluded. Methodological quality of systematic reviews was assessed using the modified R-AMSTAR tool. Meta-analysis on included primary studies was performed.
Results Only 17% of primary studies measured a clearly defined CAI population. There is strong evidence to support the contribution of dynamic balance, peroneal reaction time and eversion strength deficits and moderate evidence for proprioception and static balance deficits to non-specific ankle instability.
Conclusions Evidence from previous systematic reviews does not accurately reflect the CAI population. For treatment of non-specific ankle instability, clinicians should focus on dynamic balance, reaction time and strength deficits; however, these findings may not be translated to the CAI population. Research should be updated with an adequately controlled CAI population.
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Key Points

There is insufficient evidence to formulate accurate conclusions regarding the development of chronic ankle instability.

Dynamic balance and strength deficits should be a primary focus for the assessment of non-specific ankle instability.

1 Introduction

Worldwide, approximately 712,000 individuals sprain their ankle each day [1]. Despite placing a considerable burden on health and economic sectors [1, 2], ankle sprains are often dismissed as trivial injuries, thought to resolve quickly with minimal treatment. However, feelings of instability and recurrent ankle sprain injuries (termed chronic ankle instability, or CAI) have been reported in up to 70% of patients [3]. The subsequent development of CAI has adverse health consequences including reduced quality of life and early-onset osteoarthritis [4, 5]. Knowledge of factors that contribute to CAI and its development is therefore crucial to develop targeted intervention and prevent prolonged symptoms.

It is understood that perceived instability, mechanical laxity, and recurrent ankle sprain injuries may present independently or as comorbid attributes for individuals with CAI [6]. However, the factors contributing to CAI are still equivocal for researchers and clinicians alike. Despite considerable research, impaired balance is the only well established factor contributing to CAI [7–9]. Systematic reviews examining impaired proprioception [8–11], delayed peroneal reaction time [8, 9, 12], strength deficits [8, 13] and bone/joint characteristics [8, 14] report conflicting findings. The reasons underlying these discrepancies are unclear; however, the methodological quality of reviews and/or differences between participant selection and outcome measures of included primary studies may contribute.

Inconsistent terminology and multiple operational definitions of CAI are widespread across the literature [15]. Non-standardised participant inclusion criteria have likely influenced interpretation and limited researchers' ability to generalise current findings to a well defined CAI population. To improve transparency, the International Ankle Consortium published recommendations for inclusion of individuals with CAI and healthy participants in controlled research [16]. These participant inclusion recommendations have yet to be considered in the appraisal and synthesis of primary data within a systematic review. As a result, it is unclear whether findings of previous systematic reviews accurately reflect the CAI population.

The aim of the current systematic review was to elucidate the primary factors contributing to CAI by synthesising and evaluating the evidence from previous systematic reviews into a single meta-analysis. To determine the reason for discrepancies in the literature and directions for future research, the methodological quality of previous reviews in addition to the outcome measures and participant selection of included primary studies were considered in the analysis. It was hypothesised that differences in the methodological quality of the systematic reviews and scope of included studies would explain the inconsistent findings.

2 Methods

2.1 Protocol and Registration

The protocol review was prospectively registered with the International Prospective Register of Systematic Reviews on May 9, 2016 (Registration Number: CRD42016032592) and published online: http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-016-0275-8. The protocol and reporting adhere to PRISMA guidelines and reporting standards of systematic reviews.

2.2 Eligibility Criteria

2.2.1 Study Characteristics

To be considered for this analysis, systematic reviews needed to answer a focused research question, clearly define the search strategy criteria in addition to study selection/inclusion and complete a comprehensive search of the literature. Systematic reviews with or without meta-analysis needed to be published in a peer-reviewed journal and have compared factors associated with and/or characteristics of persons with CAI to a control group. Studies using a non-systematic review methodology (e.g. randomised controlled trials, cohort studies, case-control studies and cross-sectional studies) were excluded. Study selection was not restricted by language. Studies published in a language other than English were translated and assessed for inclusion.

2.2.2 Population

All systematic reviews and meta-analyses examining potential risk factors for ankle instability that included primary studies with a CAI population were considered for review. CAI is defined as a multifaceted condition that may present as either mechanical instability of lateral ligaments (MAI), perceived instability, recurrent ankle sprains or a combination of these factors [6, 16]. How each primary study (of the included systematic reviews) defined CAI was compared with the classification endorsed by the International Ankle Consortium [16], which is outlined in Table 1. The CAI inclusion criteria were used to assess the homogeneity of the population among primary included studies.

Table 1 International Ankle Consortium classification of CAI participants [16]

CAI inclusion/exclusion criteria
Inclusion
History of at least one significant ankle sprain that resulted in inflamation and impaired physical activity. Initial ankle sprain should occur ≥12 months prior to testing. The most recent sprain should be ≥3 months old
Two or more episodes of 'giving way' *and/or* recurrent ankle sprain *and/or* feelings of instability at the ankle that do not result in an ankle sprain
Self-reported ankle instability should be confirmed by a validated ankle instability questionnaire (e.g. the Ankle Instability Index, Cumberland Ankle Instability Tool, Identification of Functional Ankle Instability. Degree of instability should be included if relevent to research question (using the Foot and Ankle Ability Measure, or Foot and Ankle Outcome Score)
Exclusion
History of previous surgeries to musculoskeletal structures including bone, ligaments and/or nerves
History of ankle fracture in either lower limb requiring realignment
Acute injury to musculoskeletal structures (sprain, strain or fracture) in the 3 months prior to testing

CAI chronic ankle instability

Table 2 CINAHL search strategy

1	((MH "Review") OR (MH "Meta-Analysis") OR (MH "Meta-Analysis as Topic") OR systematic review OR meta-analysis OR meta analysis)
2	((MH "Ankle") OR (MH "Ankle Joint") OR (MH "Lateral Ligament, Ankle") OR ankle* OR talocrural OR talo-crural OR talo-calcaneal)
3	((MH "Ankle Injuries") OR (MH "Sprains and Strains") OR (MH "Joint Instability") OR sprain OR injur* OR instability*)
4	((MH "Cumulative Trauma Disorders") OR (MH "Chronic Pain") OR perceived OR repetitive OR functional OR mechanical OR recurrent OR repeated OR chronic)
5	1 AND 2 AND 3 AND 4

2.3 Information Sources

A comprehensive and systematic search of CINAHL, MEDLINE, PubMed, Scopus and SPORTDiscus was conducted from inception to June 1, 2017 by the primary investigator (CT). The individual search strategy for each database was created with the assistance of the Western Sydney University School of Science in Health librarian, and has been included in the previously published protocol [17]. Search terms consisted of subject headings specific to each database and free-text terms relevant to systematic review, meta-analysis, ankle joint, injuries, chronic and instability. The search strategy of CINAHL is shown in Table 2. Articles identified from the search were stored and managed using Endnote X7 throughout the review process.

2.4 Study Selection

Two reviewers (CT and RR) independently screened all articles identified from database searching. Titles of returned articles were screened based on study eligibility. Abstracts identified as potentially relevant based on the title were then assessed using the same criteria. Full texts were then screened for inclusion in the review and meta-analysis. Reference lists were hand-searched to identify additional relevant systematic reviews. Disagreement between the two reviewers was resolved by discussion to meet a consensus.

2.5 Data Item Collection and Processes

Two reviewers (CT and RR) independently extracted data from each systematic review. In the case of missing data, the corresponding author was contacted and data requested.

The data extracted included aim, search strategy, inclusion/exclusion criteria, population (sample size and participant characteristics), measurement method and outcomes related to the study aim. The homogeneity of included studies was considered with respect to their participant selection/inclusion and methods. The following data were then extracted from the individual primary studies of each systematic review to be included in the meta-analysis: authors, year of publication, outcome variables and measurement method, participant inclusion criteria, number of included participants, in addition to means and standard deviations of the outcome variable. Participant inclusion criteria of primary studies were compared

Table 3 R-AMSTAR items [18]

Items	Score
1. Was an 'a priori' design provided?	4
2. Was there duplicate study selection and data extraction?	4
3. Was a comprehensive literature search performed?	4
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	4
5. Was a list of studies (included and excluded) provided?	4
6. Were the characteristics of the included studies provided?	4
7. Was the scientific quality of the included studies assessed and documented?	4
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	1
9. Were the methods used to combine the findings of studies appropriate?	4
10. Was the likelihood of publication bias assessed?	4
11. Was the conflict of interest included?	3
Total score	**40**

R-AMSTAR Revised—A MeaSurement Tool to Assess systematic Reviews

with the International Ankle Consortium [16] recommendations outlined in Table 1.

2.6 Risk of Bias and Methodological Quality Assessment

Independent critical appraisal and data extraction were completed by two reviewers (CT and RR). Disagreement was resolved by discussion to reach a consensus.

Systematic review quality and potential bias were assessed using the modified R-AMSTAR tool (Revised—A MeaSurement Tool to Assess systematic Reviews). A detailed version of the modified R-AMSTAR is available online: (https://static-content.springer.com/esm/art%3A10.1186%2Fs13643-016-0275-8/MediaObjects/13643_2016_275_MOESM3_ESM.pdf) and attached as an additional file of the protocol paper [17]. A summary of the R-AMSTAR tool is shown in Table 3. Using the modified R-AMSTAR, studies were given a score out of 40. A higher score indicated higher methodological quality, greater internal validity and lower risk of bias. The methodological quality of systematic reviews was ranked from highest to lowest based on total score and percentile (rank: A 90–100%, B 80–89%, C 70–79%, D 60–69%, E <60%). Impacts of bias and methodological flaws on the internal validity of the review were considered in the synthesis of review findings. Reviews were not excluded based on quality.

2.7 Data Synthesis and Analysis

The percent agreement between reviewers regarding eligibility screening and methodological quality of systematic reviews was calculated using kappa scores of agreement.

A meta-analysis of included primary studies from systematic reviews of the same methodological quality was performed, if outcomes were comparable. To avoid confounding from inclusion of the same individual primary studies by multiple systematic reviews, averages and standard deviations of individual studies were extracted instead of the total mean difference calculated by the reviews. Duplicate studies were then removed. Heterogeneity was assessed using the chi-square (I^2) calculation and interpreted as 0–40% representing unimportant heterogeneity, 41–60% moderate heterogeneity, 61–90% substantial heterogeneity and 91–100% considerable heterogeneity [19]. A random-effects model was used on all heterogeneous data ($I^2 > 40\%$). Findings not suitable for meta-analyses were summarised qualitatively. Sub-group analyses were performed with respect to the International Ankle Consortium inclusion/exclusion criteria for CAI research [16], the method used to measure outcomes and organised by methodological quality of the systematic review. All meta-analyses were conducted in RevManager version 5.0 (Copenhagen, Denmark: the Nordic Cochrane Centre, the Cochrane Collaboration, 2008). Standard mean difference (SMD) and 95% confidence intervals (CIs) were calculated. An SMD of 0.3, 0.5 and 0.8 indicated a weak, moderate and strong effect size, respectively. Given the significant heterogeneity within the data, prediction intervals (PIs) were calculated to estimate the uncertainty around the effect estimate. A Spearman's rank correlation coefficient (Spearman's *rho*) was calculated between R-AMSTAR score and effect size, in addition to R-AMSTAR score and significance ($p > 0.05$, or $p < 0.05$). A Mann–Whitney *U* test for non-parametric data was used to compare R-AMSTAR scores between meta-analyses reporting significant findings and those reporting non-significant findings.

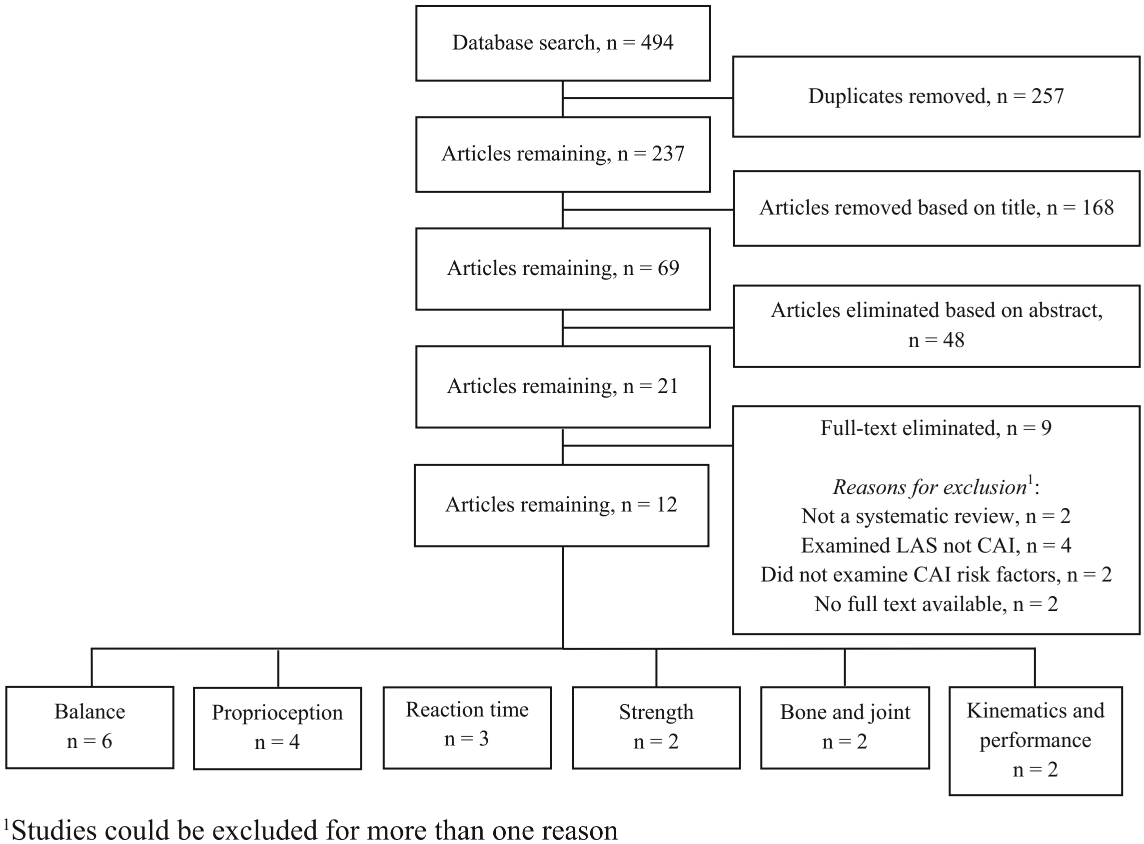

Fig. 1 Search strategy results. *CAI* chronic ankle instability, *LAS* lateral ankle sprain

3 Results

3.1 Study Selection

Database searching returned 492 potential articles. Numbers of studies screened, assessed for eligibility and included in the review, are shown in Fig. 1. A total of twelve systematic reviews were included. Inter-rater kappa scores of agreement were high for both screening of abstracts ($k = 0.947$, $SE = 0.52$) and full-text articles ($k = 0.957$, $SE = 0.42$). The percent agreement for admissibility of systematic reviews during full-text critical appraisal was 91% (10/11). Consensus regarding inclusion of reviews was reached through discussion between the two primary reviewers (CT and RR) and did not require further deliberation from a third, independent reviewer.

3.2 Study Characteristics

Six included systematic reviews evaluated dynamic and/or static balance [7–9, 20–22], four examined proprioception [8–11], three studied reaction time [8, 9, 12], two analysed strength [8, 13], bone and joint characteristics [8, 14] and biomechanical differences [8, 23] and one reviewed functional performance factors [8]. The outcomes investigated, number of included studies, meta-analysis summary and modified R-AMSTAR scores of each review are presented in Tables 4 and 5. Three systematic reviews examined 'general lateral ankle trauma', with the inclusion of both chronic and acute ankle instability in the analysis [12, 20, 21]. Reasons for exclusion of nine seriously considered reviews were as follows: four examined acute lateral ankle sprains only [24–27], two were not a systematic review [28, 29], two did not examine CAI risk factors [30, 31] and two had no full-text available [31, 32].

3.3 Risk of Bias Within Studies

R-AMSTAR rank (Table 4) was weakly correlated with both effect size and significance (Spearman's rho <0.40). R-AMSTAR rank did not differ between meta-analyses reporting significant (mean 7.45) and non-significant findings (mean 9.10, $U = 19.50$, $Z = -0.81$, $p = 0.51$). Thus, the methodological quality of each systematic review was not a strong predictor of overall effect or significance. Qualitative syntheses of review findings, which are stratified according to risk of bias within reviews, are provided in Electronic Supplementary Material (ESM) Appendix S1.

Table 4 R-AMSTAR scores: total and rank [18]

Study	Modified R-AMSTAR item													
	1	2	3	4	5	6	7	8	9	10	11	Total	%	Rank
Arnold et al. 2009 [7]	3	4	4	3	2	4	4	1	4	4	3	36	90.00	A
Arnold et al. 2009 [13]	3	4	4	3	2	4	2	1	3	4	1	31	77.50	C
Wikstrom et al. 2010 [20]	3	4	4	1	4	4	3	0	2	4	2	31	77.50	C
Hoch and McKeon 2014 [12]	3	1	4	2	3	4	3	1	1	4	3	29	72.50	C
McKeon and McKeon 2012 [10]	3	1	3	1	3	4	4	1	3	4	1	28	70.00	C
Moisan et al. 2017 [23]	4	4	3	2	2	4	3	1		1	2	26	72.22	C
Song et al. 2016 [22]	3	1	5	1	2	4	1	0	4	3	3	26	65.00	D
Hiller et al. 2011 [8]	3	4	4	1	2	4	1	0	3	1	3	26	65.00	D
Wikstrom et al. 2009 [21]	3	2	4	1	3	3	1	0	2	3	3	25	62.50	D
Munn et al. 2010 [9]	3	2	4	2	2	4	2	0	3	1	1	24	60.00	D
Wright and Arnold 2011 [11]	3	1	3	3	2	4	2	1		1	1	21	58.33	E
Cordova et al. 2010 [14]	3	1	3	1	3	4	2	0		1	1	19	52.78	E
Average	3.08	2.31	3.69	1.69	2.54	3.92	2.31	0.46	2.60	2.46	1.92	30.17	67.37	D

R-AMSTAR Revised—A MeaSurement Tool to Assess systematic Reviews

3.4 Meta-Analysis of Individual Primary Studies

A summary of total effect sizes for subgroup analyses, in addition to respective 95% CIs and PIs, is provided for each outcome in Fig. 2a–e. The SMD and 95% CI of individual, primary studies are provided in ESM Appendix S2. Data from one study measuring time to stabilisation (TTS) could not be extracted from the individual primary study [33]—the authors were contacted; however, the data could not be located. No meta-analysis was performed on bone and joint characteristics, biomechanics and functional performance outcomes due to insufficient homogeneity regarding protocols and measures (task requirements, conditions, outcomes examined and/or analysis).

3.4.1 Heterogeneity

Given substantial heterogeneity within (overall, $I^2 = 78\%$) and between static balance measures (area, $I^2 = 85\%$; linear, $I^2 = 52\%$; time, $I^2 = 74\%$; velocity, $I^2 = 82\%$; and other, $I^2 = 79\%$), a random-effects analysis was used to determine the extent of balance deficits in CAI. A fixed-effect analysis was performed on the Star Excursion Balance Test (SEBT) as low heterogeneity was observed within this subgroup ($I^2 = 0\%$). A 95% PI was not calculated for the SEBT due to the lack of heterogeneity. A separate random-effects analysis was performed on TTS study measures due to substantial heterogeneity between included primary studies ($I^2 = 63\%$). For proprioception outcomes, a random-effects analysis was used to determine the extent of the active absolute error ($I^2 = 84\%$) and passive absolute error ($I^2 = 41\%$) subgroups; however, a fixed-effect model was used for passive movement detection ($I^2 = 0\%$). No meta-analysis was performed on total error for both passive and active joint position sense (JPS) in view of an insufficient number of included studies. For reaction time and strength outcomes, a random-effects analysis was used in view of substantial heterogeneity (all subgroups, $I^2 > 81\%$).

3.4.2 Factors Demonstrating a Strong Effect in Ankle Instability Compared to Controls

For balance, a significant effect was observed between groups for dynamic time-to-stabilisation measures only (SMD 1.02; 95% CI 0.64–1.40; 95% PI 0.07–1.89; $Z = 5.24$; $p < 0.001$). In addition, there was strong evidence to support delayed reaction time in people with chronic ankle instability (SMD 0.82; 95% CI 0.48–1.15; 95% PI −0.53 to 2.17; $Z = 4.91$; $p < 0.001$). However, sub-group analyses for reaction time data indicated a strong, significant effect only for peroneus brevis reaction time (SMD 1.23; 95% CI 0.32–2.14; 95% PI −5.68 to 8.14; $Z = 2.65$; $p = 0.008$) and reaction time at 30° of inversion (SMD 1.42; 95% CI 0.86–1.98; 95% PI –0.84 to 3.68; $Z = 4.95$; $p < 0.001$). A significant difference between people with CAI and controls was found for both concentric eversion (SMD –1.61; 95% CI −2.80 to −0.43; 95% PI −7.51 to 4.29; $p = 0.001$) and eccentric eversion peak torque (SMD −1.62; 95% CI −2.81 to −0.43; 95% PI −14.14 to 10.91; $p = 0.008$).

Table 5 Characteristics of included systematic reviews

Outcome variable	Systematic review	Aim	Modified R-AMSTAR		Number of included studies	Measure(s)	Meta-analysis summary
			Total	Rank			
Static balance	Arnold et al. 2009 [7]	1. To determine overall difference in static balance between healthy and CAI 2. To determine if different measures have an effect	36	A	4	Time in balance	Impaired (SMD 1.82, 95% CI 0.80–2.83)
					14	SLS velocity	Impaired (SMD 0.23, 95% CI 0.05–0.41)
					6	SLS area	No difference (SMD 0.24, 95% CI –0.08 to 0.57)
					13	SLS linear AP/ML	Impaired (SMD 0.45, 95% CI 0.16–0.74)
					6	Other	Impaired (SMD 1.035, 95% CI 0.14–1.93)
					19	Total	Impaired (SMD 0.32, 95% CI 0.19–0.46)
	Wikstrom et al. 2010 [20]	To identify the presence of bilateral balance impairments in unilateral CAI	31	C	12	Involved ankle	Impaired (SMD 0.45, 95% CI 0.27–0.63)
						Uninvolved ankle	Impaired (SMD 0.28, 95% CI 0.10–0.45)
	Song et al. 2016 [22]	To examine differences in visual utilisation during balance in CAI and healthy controls	25	D	11	Time to boundary; eyes open and eyes closed	CAI participants (SMD -2.04, 95% CI -2.31 to -1.77) Healthy participants (SMD -1.50, 95% CI -1.71 to -1.29)
	Hiller et al. 2011 [8]	To identify differences in physical factors, strength, stability, proprioception, reaction time, biomechanics and functional tests	26	D	9	Stable surface, eyes open (COP, sway)	No difference (SMD 0.40, 95% CI 0.00–0.70)
						Stable surface, eyes closed (COP, sway)	Impaired (SMD 0.90, 95% CI 0.40–1.40)
						Unstable surface, eyes open (COP, sway)	Impaired (SMD 0.50, 95% CI 0.10–1.00)
	Wikstrom et al. 2009 [21]	To identify postural control impairment in CAI	25	D	25	BESS, COP	Impaired (ES = 0.49, 95% CI 0.40–0.59)
	Munn et al. 2010 [9]	To identify key sensorimotor factors in CAI	24	D	10	SLS velocity and area	Impaired (SMD 0.60, 95% CI 0.20–1.00)

Table 5 continued

Outcome variable	Systematic review	Aim	Modified R-AMSTAR		Number of included studies	Measure(s)	Meta-analysis summary
			Total	Rank			
Dynamic balance	Arnold et al. 2009 [7]		36	A	4	SEBT	Impaired (SMD 0.29, 95% CI 0.19–0.39)
					4	TTS	Impaired (SMD 0.61, 95% CI 0.38–0.84)
					8	Total	Impaired (SMD 0.34, 95% CI 0.25–0.41)
	Munn et al. 2010 [9]		24	D	4	Anterior-posterior TTS	Impaired (MD = 0.70, 95% CI 0.40–1.00)
					4	Medio-lateral TTS	Impaired (MD = 0.60, 95% CI 0.40–0.80)
					4	SEBT	Impaired (SMD 0.40, 95% CI 0.10–0.70)
Proprioception	McKeon and McKeon 2012 [10]	To determine the most consistent joint position recognition variables for identifying deficits	28	C	6	Passive JPS	Impaired (SMD 0.46, 95% CI 0.32–0.60)
					7	Active JPS	Impaired (SMD 0.57, 95% CI 0.29–0.86)
	Hiller et al. 2011 [8]		26	D	3	Passive JPS	No difference (SMD 0.20, 95% CI -0.30 to 0.80)
					3	Active JPS	No difference (SMD 1.20, 95% CI -0.30–2.60)
					3	Passive mixed inversion/eversion	No difference (SMD 0.70, 95% CI -0.20 to 1.60)
	Munn et al. 2010 [9]		24	D	6	Passive JPS	Impaired (MD 0.70°, 95% CI 0.20–1.20)
					10	Active JPS	Impaired (MD 0.60°, 95% CI 0.20–1.00)
					6	PMD	No meta-analysis performed (DNH)
	Wright and Arnold 2011 [11]	To identify eversion force sense deficits in CAI	21	E	7	Eversion force sense	No meta-analysis performed (ES not significant)

Table 5 continued

Outcome variable	Systematic review	Aim	Modified R-AMSTAR Total	Modified R-AMSTAR Rank	Number of included studies	Measure(s)	Meta-analysis summary
Reaction time	Hoch and McKeon 2014 [12]	To identify deficits in CAI	29	C	13	Peroneal RT	Impaired (ES 1.04, 95% CI 0.68–1.41)
	Hiller et al. 2011 [8]		26	D	4	Peroneal RT	No difference (MD 3.30, 95% CI -2.30 to 8.90)
	Munn et al. 2010 [9]		24	D	11	Peroneal RT	No difference (MD 7.80, 95% CI -1.40 to 17.1)
Strength	Arnold et al. 2009 [13]	To identify eversion force sense weakness in CAI, and the influence of testing velocity	31	C	12	Concentric eversion	Impaired (SMD 0.22, 95% CI 0.12–0.33)
	Hiller et al. 2011 [8]		26	D	4	Concentric eversion	No difference (SMD 1.89, 95% CI -0.0 to 3.90)
					5	Eccentric eversion	No difference (SMD 1.95, 95% CI -0.05 to 3.95)
					4	Concentric inversion	Impaired (SMD 1.10, 95% CI 0.20–2.10)
					3	Eccentric inversion	No difference (SMD 1.50, 95% CI −1.00 to 3.50)
Bone and joint	Hiller et al. 2011 [8]		26	D	10	Anatomical, ROM, joint laxity, stiffness	No meta-analysis performed (DNH)
	Cordova et al. 2010 [14]	To determine the effect of CAI on joint laxity	19	E	4	Anterior joint laxity	No meta-analysis performed (ES of 3 studies significant)
					3	Posterior joint laxity	No meta-analysis performed (ES of 1 study significant)
					8	Inversion joint laxity	No meta-analysis performed (ES of 3 studies significant)
					3	Eversion joint laxity	No meta-analysis performed (ES not significant)
Biomechanics	Hiller et al. 2011 [8]		26	D	20	Kinematics, kinetics, TTS	No meta-analysis performed (DNH)
	Moisan et al. 2017 [23]	To determine whether participants with CAI have altered gait patterns	26	C	24	Kinematics, kinetics, electromyography	No meta-analysis performed (DNH)
Functional performance	Hiller et al. 2011 [8]		26	D	5	Agility, jump height, hopping tests, shuttle run	No meta-analysis performed (DNH)

AP anteroposterior, *BESS* Balance Error Scoring System, *CAI* chronic ankle instability, *CI* confidence interval, *COP* centre of pressure, *DNH* data not homogenous, *ES* effect size, *JPS* joint position sense, *MD* mean difference, *ML* mediolateral, *PMD* passive movement detection, *R-AMSTAR* R(evised)–A MeaSurement Tool to Assess systematic Reviews, *ROM* range of motion, *RT* reaction time, *SEBT* Star Excursion Balance Test, *SLS* single leg sway, *SMD* standard mean difference, *TTS* time to stabilisation

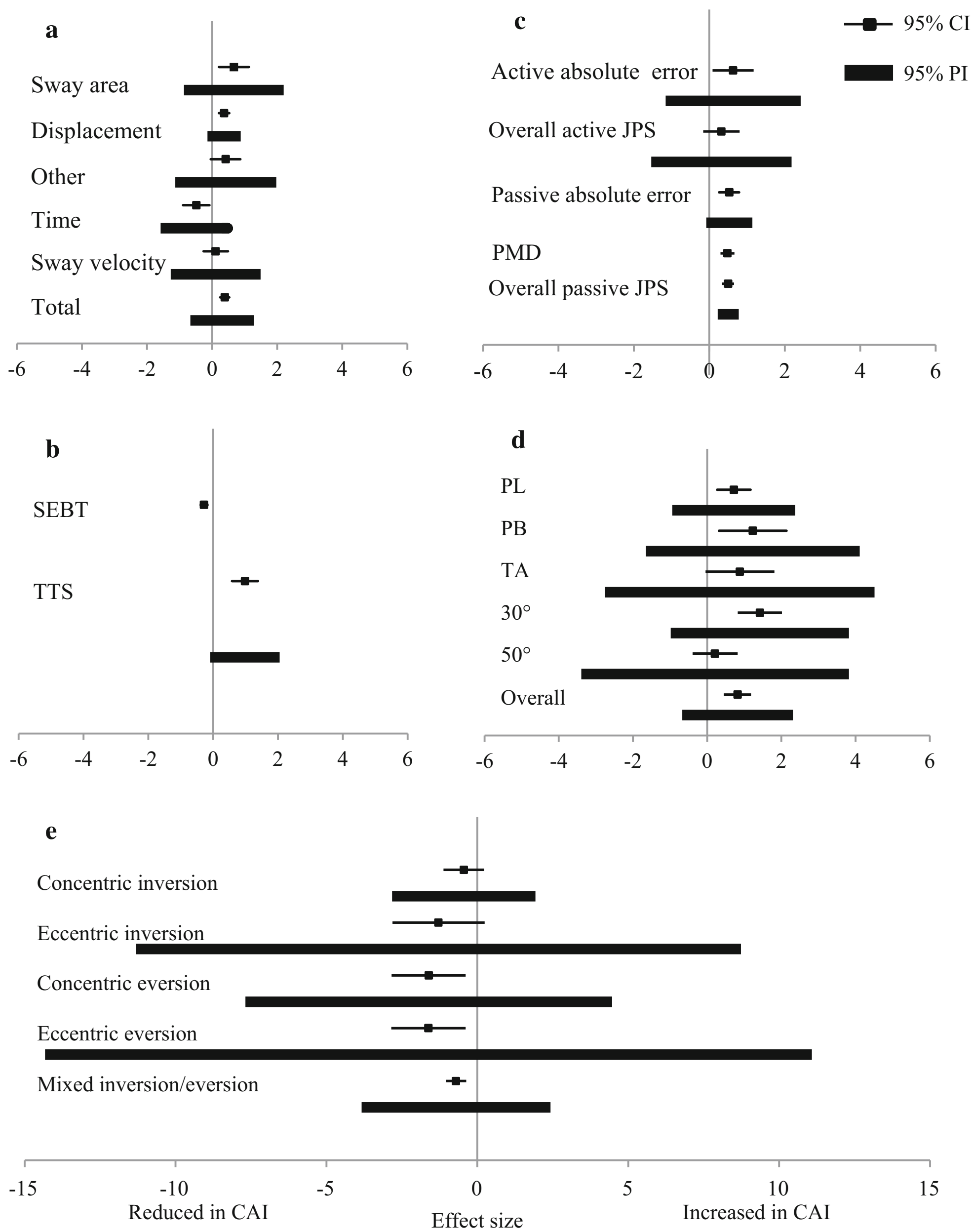

Fig. 2 Meta-analysis summaries: confidence and prediction intervals. Findings represent SMD with 95% CI and PI of static balance (**a**), dynamic balance (**b**), proprioception (**c**), reaction time (**d**) and strength measures (**e**). *CAI* chronic ankle instability, *CI* confidence interval, *JPS* joint position sense, *PB* peroneus brevis, *PI* prediction interval, *PL* peroneus longus, *PMD* passive movement detection, *SEBT* Star Excursion Balance Test, *SMD* standard mean difference, *TA* tibialis anterior, *TTS* time to stabilisation

3.4.3 Factors Demonstrating a Moderate Effect in Ankle Instability Compared to Controls

There was moderate evidence to suggest static balance was impaired, compared with controls, using measures of sway area (SMD 0.62; 95% CI 0.19–1.05; 95% PI −0.68 to 1.91; $Z = 2.82$; $p = 0.005$). Similarly, moderate evidence was present for proprioceptive measures of active (SMD 0.62; 95% CI 0.27–0.96; 95% PI −0.97 to 2.21; $Z = 3.53$; $p < 0.001$) and passive absolute error (SMD 0.53; 95% CI 0.26–0.79; 95% PI 0.06–1.00; $Z = 3.88$; $p < 0.001$). Further proprioceptive analyses based on direction tested demonstrated weak effects during passive eversion (SMD 0.59; 95% CI 0.30–0.87; $p < 0.01$). For reaction time measures, sub-group analyses based on muscle investigated showed a significant, moderate delay in peroneus longus

(SMD 0.72; 95% CI 0.27–1.17; 95% PI –0.80 to 2.24; $Z = 3.11$; $p = 0.002$). A significant–moderate effect was also found for strength. More specifically, overall reduced peak torque in the CAI was reduced in total concentric/eccentric inversion and eversion peak torque (SMD −0.71; 95% CI −1.00 to −0.41; 95% PI −3.67 to 2.25; $Z = 4.73$; $p < 0.001$).

3.4.4 *Factors Demonstrating a Weak Effect in Ankle Instability Compared to Controls*

Static balance sub-group analyses produced significant, yet weak effects for linear sway displacement (SMD 0.37; 95% CI 0.21–0.53, 95% PI 0.02–0.72; $Z = 4.60$; $p < 0.001$) and time to boundary measures (SMD −0.45; 95% CI −0.77 to −0.14; 95% PI −1.23 to 0.33; $Z = 2.83$; $p = 0.005$). A weak, significant effect was also found for total dynamic SEBT measures in all directions (SMD −0.28; 95% CI −0.38 to −0.18, $Z = 5.62$; $p < 0.001$). However, a sub-analysis based on direction indicated that only anteromedial (SMD −0.35; 95% CI −0.67 to −0.04; $p = 0.03$), medial (SMD −0.36; 95% CI −0.865 to −0.07; $p = 0.01$), posteromedial (SMD −0.36; 95% CI −0.62 to −0.09; $p = 0.009$) and anterolateral directions (SMD −0.34; 95% CI −0.65 to −0.02; $p = 0.04$) were significant. For proprioceptive measures, passive movement detection (SMD 0.48; 95% CI 0.33–0.63; $Z = 6.28$; $p < 0.001$) and overall passive joint position sense (passive SMD 0.45; 95% CI 0.32–0.58; $Z = 3.43$; $p < 0.001$) effects were also weak. Sub-group analyses on proprioceptive measures utilising active *absolute* joint position sense measures (active absolute SMD 0.32; 95% CI −0.13 to 0.77; 95% PI −1.03 to 2.28; $Z = 1.39$; $p = 0.17$) again yielded weak results. Further proprioceptive analyses demonstrated weak effects during passive inversion directions (SMD −0.34; 95% CI 0.18–0.50; $p < 0.01$). Finally, a significant-weak effect was found for reaction time delays in CAI at 50 ° of inversion (SMD 0.21; 95% CI −0.36 to 0.79; 95% PI −3.26 to 3.68; $Z = 0.72$; $p = 0.47$).

3.4.5 *Factors Demonstrating No Difference Between Ankle Instability and Controls*

For static balance, measures of sway velocity and 'other' (i.e. time in balance and number of foot lifts during single-limb stance) were not different between groups (sway velocity, $p = 0.56$; other, $p = 0.07$). No difference was observed in anterior, posterior, lateral and posterolateral reach distance between groups using the SEBT ($p \geq 0.05$). Similarly, proprioceptive measures of active ($p = 0.17$) and total mixed inversion/eversion joint position sense were not significant ($p = 0.24$). For reaction time, no significant delay was observed in tibialis anterior ($p = 0.16$). Only one primary study examined differences in extensor digitorum reaction time, and therefore a meta-analysis was not performed; however, no differences between groups were observed in this study. Within-muscle comparisons over varying degrees of inversion were not performed due to insufficient study numbers. For strength measures, sub-analyses showed no significant difference for inversion strength (concentric inversion, $p = 0.10$; eccentric inversion, $p = 0.09$).

3.4.6 *Effect of Participant Selection*

Of 77 included primary studies, 13 provided adequate descriptions of participant inclusion criteria (17%). Included primary studies and those that met International Ankle Consortium recommendations for each outcome are provided in Table 6. Reasons for studies failing to meet the International Ankle Consortium [16] recommendations included (1) did not use, or provide information on, an adequate tool to identify/classify CAI severity and/or CAI group likely included acute/coper ankle sprain injuries (58%); (2) absence of a healthy control group, that is, included between-limb comparisons or CAI participants post-surgery (31%); (3) failed to provide sufficiently detailed inclusion/exclusion detail for either the CAI or control groups (28%). Due to an insufficient number of studies with appropriate definition of groups (CAI and

Table 6 Percentage of studies that met participant selection recommendations for each outcome

Outcome	Number of studies	References		%
		All primary studies	Met criteria	
Static balance	35	[27, 34–67]	[46, 47, 53, 62, 64–67]	23
Dynamic balance	10	[35, 37, 38, 53, 62, 68–73]	[37, 53, 62, 71, 72]	50
Proprioception	14	[39, 45, 73–84]		0
Reaction time	15	[85–99]	[87]	6
Strength	14	[37, 55, 76, 80, 100–109]	[108]	7

control), the influence of inclusion criteria on proprioception, reaction time and strength outcomes could not be calculated.

A random-effects analysis was performed on overall static balance across the six studies that met the participant inclusion criteria ($I^2 = 68\%$). Removal of static balance studies with inadequately described inclusion criteria reduced SMD and 95% CI for static balance measures (SMD_{total} 0.26; 95% CI 0.12–0.43 vs $SMD_{removed}$ 0.13; 95% CI −0.07 to 0.33); however, the PI was reduced (95% PI_{total} −0.49 to 1.27 vs 95% $PI_{removed}$ −0.12 to 0.41), reflecting reduced heterogeneity and improved ability to predict findings in future studies. Only one study did not meet the recommended guidelines for inclusion of CAI and healthy control groups among the dynamic TTS studies [35]. Removal of the one study that did not meet inclusion criteria increased the calculated effect size (SMD_{total} 0.98 vs $SMD_{removed}$ 1.29).

4 Discussion

The findings of the current review indicated that balance, proprioception, reaction time and strength are impaired in ankle instability compared with healthy controls. However, strong effects were found for dynamic balance (quantified as TTS), peroneal reaction time and eversion strength measures only. Discrepancies between previously published systematic reviews regarding the contribution of these factors to ankle instability were not explained by review quality, but more likely resulted from methodological differences (i.e. heterogeneous participant inclusion and outcome measures) between included primary studies. Due to heterogeneous participant inclusion among primary studies, the CAI population was not well represented in the literature—only 17% of included primary studies clearly defined a chronically unstable population in accordance with the inclusion guidelines [16]. Time-to-stabilisation was the only outcome studied in a well-defined CAI population. Thus, findings for all other outcomes better generalise to a non-specific 'history of ankle sprain' population; that is, a combination of CAI, acute ankle instability and copers. Based on this evidence, the contributions of static balance, reaction time, proprioception and strength deficits to a well defined CAI population are still unclear.

4.1 Clinical and Research Implications

4.1.1 Factors with Evidence of a Strong Contribution to Ankle Instability

There is strong evidence of a multifactorial contribution to ankle sprain injuries. Impaired balance, reaction time and strength likely contribute to ankle instability by reducing an individual's ability to stabilise the ankle joint against inversion sprain. Moreover, prolonged TTS, delayed peroneal reaction time and reduced eversion strength likely contribute to ankle instability; thus, tests to routinely assess these factors should be considered. Improving dynamic balance, reaction time and strength should thus be primary targets for rehabilitation of ankle instability.

In the current review, the calculated effect of TTS was stronger than that of previous meta-analyses [7, 9]. The stronger calculated effect was likely due to missing data from one primary study which could not be included in the meta-analysis of the current review [33]. Various TTS calculation methods (differences in trial length, sampling rate and filtering method) employed by the included primary studies likely contributed to the large heterogeneity observed in the data [110]. Irrespective of multiple calculation methods, TTS is a sensitive indicator of dynamic balance in those with CAI, with useful research applications. However, such a measure is understandably difficult to implement routinely in clinical settings. The development of a valid and simple measure which replicates the TTS task (e.g. time in single-leg stance following a landing) has potential to translate into, and improve the sensitivity of, clinical assessment in this population.

Testing method and muscle investigated are important considerations for reaction time measures in primary research. Pooled findings from the current review suggest that reaction time deficits occur up to a threshold of 30° inversion—after which peroneal muscle activation is likely delayed in both healthy participants and participants with ankle instability. Lower degrees of inversion are thus needed to sensitively measure reaction time deficits. Reducing the inversion angle may also have positive safety implications. Pooled data from the current review also suggest that reaction time deficits are specific to the peroneal musculature. Delayed peroneal reaction time in ankle instability was corroborated by one previous systematic review [12], whereas two found no difference [8, 9]. Reviews that found peroneal reaction time was not delayed in ankle instability had earlier publication dates and thus included fewer primary studies, which may explain these discrepancies. Sub-group analyses by Hoch and McKeon [12] demonstrated strong effects for delayed peroneal reaction time in CAI and weak effects in acute lateral ankle sprain populations. This finding may support the presence of delayed reaction time in CAI, but not acute ankle sprain injury. However, as the current review found that only one primary study of peroneal reaction time met the International Ankle Consortium inclusion criteria, the extent of reaction time deficits in CAI are still unclear and these findings may better generalise to a non-specific, history-of-ankle-sprain population.

Previous reviews have found both strong [8] and weak [13] effects for reduced evertor strength in ankle instability. This discrepancy was likely due to one review using more stringent inclusion criteria for primary studies based on the CAI definition [8]. Consideration of the available evidence revealed a significant, strong effect for evertor weakness. Evertor weakness is thus potentially an important and modifiable factor in ankle instability rehabilitation. Following strength training, spinal and supraspinal neural adaptation mechanisms result in an increase in motor neuron output and firing rate [111, 112]. As a result, strength training may also have positive implications for commonly observed sensorimotor deficits (i.e. such as the delayed peroneal reaction time) in ankle instability patients. As similar observations of altered muscle activation have also been observed superior to the ankle joint in CAI [113], development of a whole-body strengthening programme may be beneficial in this population.

4.1.2 Factors with Moderate Contribution to Ankle Instability

There is only moderate evidence to support the contribution of static balance and proprioceptive deficits to ankle instability. The findings of this review suggest that static balance and proprioception are not likely to be sensitive measures of non-specific ankle instability deficits.

The current review found a moderate effect for reduced static balance using sway area measures in ankle instability. A previous review showed that static balance with eyes closed and/or unstable conditions produced large static postural sway deficits in ankle instability patients [8]. However, it is important to note that the number of studies examining either stable, unstable, eyes open and/or closed conditions was small. Post-hoc power calculations of these included studies were also variable, with most studies being weak to moderately powered (studies $n = 3$; total participants $n = 41$; power $1-\beta = 0.14$–0.98). A more recent meta-analysis of 11 studies indicated that both healthy individuals and those with CAI have significantly impaired postural stability during static, eyes-closed conditions [22]. Although static balance tasks are a simple clinical assessment tool, they may not be a sensitive indication of instability or recovery without visual occlusion. However, even with visual occlusion there is still limited evidence to suggest static balance is a sensitive comparison between healthy and CAI populations (a more in-depth discussion is provided in ESM Appendix S1). More challenging dynamic stability tasks may therefore be preferable as a clinical assessment tool.

Joint position sense deficits were previously shown to be significantly impaired in those with ankle instability, regardless of measurement differences such as between-group or between-limb comparison, starting foot position, repositioning method (active or passive), range of motion and testing velocity [9, 10]. Despite identifying statistically significant deficits, the current review found the effect of proprioceptive deficits to be weak to moderate only. Given the large number of studies included, we propose that this is not likely due to underpowered studies and/or insufficient data, but rather because such measures of proprioception are not sufficiently sensitive to detect deficits. Current methods utilised to measure proprioception do not replicate conditions under which ankle sprains occur. The ecological validity of current proprioceptive measures to assess ankle instability is therefore questionable and could explain why proprioception is not a strong indicator of ankle instability. For this reason, future research may consider examining proprioception at speeds which mimic ankle inversion sprains or alternate methods for probing proprioceptive afferents.

4.1.3 Factors with Weak/No Contribution to Ankle Instability

There is insufficient evidence to support static balance deficits using measures of linear sway displacement, velocity and time to boundary measures. Furthermore, assessing dynamic balance deficits using the SEBT, proprioception using passive movement detection and/or joint position sense, and strength using inversion torque are also weakly supported. Thus, clinicians and researchers should be aware that such tools are not useful indicators of ankle instability.

4.2 Limitations and Future Directions

Eighty-three percent of the included primary literature did not meet the desired CAI inclusion criteria [16]. Sub-analyses based on inclusion criteria performed by the current review demonstrate that incorrect classification contributes to avoidable heterogeneity, likely influences calculated effects and limits future applicability. Large PIs were calculated for all outcomes, reflective of the considerable heterogeneity present between primary studies. PIs complement confidence intervals by estimating the range of expected effects in future studies [114, 115]. Based on the calculated PIs, all outcome measures are unlikely to show significance if future CAI research continues with poor standardisation of participant inclusion criteria. Updated research with adequately controlled participant selection, reflective of the CAI population, is therefore necessary to understand the foundation of CAI development and its contributing factors.

Measurements of contributing factors in this population have focused on clinical and functional outcomes. Balance, proprioception and reaction time have been used to indirectly assess deficits in sensorimotor control, but the mechanisms behind these deficits are still unclear. Passive proprioceptive tests and active proprioceptive tests bias joint and musculotendinous mechanoreceptors, respectively [116]. The weak to moderate effects found for proprioception measures may suggest that such deficits are specific to the motor portion of the sensorimotor pathway. Mechanisms of neuromuscular control mediated by the sensorimotor pathway have yet to be comprehensively examined in this population. Emerging research suggests that neuromuscular control may be altered at both a spinal and supra-spinal level [117–120]. Identifying these mechanisms will likely assist the development of more targeted rehabilitation programmes for CAI.

The authors acknowledge that much of the research included in this review was published prior to the International Ankle Consortium statement regarding inclusion of CAI participants [16]. All reviews that included primary studies on a CAI population were considered in this review. Systematic reviews examining a 'history of ankle sprain' [12, 20, 21] and not specifically CAI were therefore also included. Although this is a systematic review of systematic reviews, the critique and analysis based on participant inclusion were performed on primary studies and separately to the aims of the reviews themselves. This approach is consistent with the aims of the current review. The authors acknowledge that a large body of evidence has been published following these reviews which may also impact the conclusions of this study.

5 Conclusion

Ankle instability is a multi-faceted condition that incorporates dynamic balance, peroneal reaction time and eversion strength deficits. All factors contributing to ankle instability should be considered in a holistic, rehabilitative treatment to better target this condition and reduce the health and economic burden. Unfortunately, the common reporting of inadequately detailed inclusion criteria across primary studies limits interpretation and applicability of the current research to the CAI population. The identified deficits in balance, reaction time and strength outcomes provide further evidence for deficits in sensorimotor control and potentially central drive mechanisms. Further mechanism-specific research of central processing (afferent and cortical drive) that incorporates the recommended inclusion criteria may improve understanding of CAI and contribute to the development of targeted rehabilitation protocols.

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Compliance with Ethical Standards

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